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SOLUTION FOR TRANSPLANTATION ORGAN

[□□□□□□□]

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(57) [Abstract]

[Constitution]

solution. for transplantation organ which in 1000 ml aqueous solution, trehalose 50 - 240 mM, Na^+ 10 - 140 mM, K^+ 4 - 140 mM, Mg^{++} 0 - 4 mM, Ca^{++} 0 - 2 mM, $H_2PO_4^-$ or HPO_4^{--} 12 -65 mM, Cl^-, HCO^-, CO_3^{--}, organic acid or organic acid anion 0 - 80 g contains 15 - 150 mM, hydroxyethyl starch, osmotic pressure with 270 - 450 mOsm/l pH 7 - 8 is

[Effect (s)]

Without impairing functions of organ for transplant, perfusion and lengthy preservation to be possible, furthermore

solution for the stable transplantation organ can be offered to pharmaceutical.

[Claim (s)]

[Claim 1]

solution. for transplantation organ which designates that in 1000 ml aqueous solution, it contains below-mentioned component at least inside below-mentioned range, osmotic pressure with 270 - 450 mOsm/l pH 7 - 8 it is as feature

５０～２４０ｍＭ
50 - 240 mM
１０～１４０ｍＭ
10 - 140 mM
４～１４０ｍＭ
4 - 140 mM
０～４ｍＭ
0 - 4 mM
０～２ｍＭ
0 - 2 mM
１２～６５ｍＭ
12 - 65 mM

トレハロース

trehalose

Ｎａ＋

Na+

Ｋ＋

K+

Ｍｇ＋＋

Mg ++

C a++
Ca ++
H2 P O4 - 又はH P O4
H2PO4- or HPO4
0 - 80 g

[Description of the Invention]

[0001]

[Field of Industrial Application]

this invention regards solution for transplantation organ, furthermore details regard solution which is used because perfusion or it retains organ for transplant.

[0002]

[Prior Art]

In one of solution for transplantation organ which from until recently is well used in Europe and America, there is a Euro-Collins (Euro-Collins) solution which contains potassium chloride, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, sodium hydrogen carbonate and fructose.

But, although it can utilize in kidney whose function maintenance power is high, protective action for degeneration of cell concerning other organ the satisfactory cannot call this solution, there is a problem that holding time of organ function is short.

Recent, as non- permeant hydroxyethyl starch was contained as lactobionic acid sodium and the raffinose, and glutinous osmotic pressure agent, furthermore energy metabolism of cell was considered and electrolyte solution, UW solution (Japan Unexamined Patent Publication Hei 1- 246201 disclosure) where it can add adenosine and insulin, etc., was developed.

But, this solution is a difficulty in pharmaceutical stability, is a or other problem which needs the low temperature storage.

[0003]

[Problems to be Solved by the Invention]

Therefore, problem of this invention, in solution because perfusion or it retains organ for transplant, in maintenance action of organ function to be superior, furthermore to pharmaceutical stable solution to offer it is.

[0004]

[Means to Solve the Problems]

As for these inventors, result of diligent investigation, it could complete this invention which solves above-

mentioned problem making use of various electrolyte, osmo-regulator, glutinous osmotic pressure agent and the plasma membrane stabilizer, concerning those combinations and proportion.

[0005]

namely, this invention, in 1000 ml aqueous solution, contains below-mentioned component at least inside below-mentioned range, osmotic pressure pH 7 - 8 is something which offers solution for transplantation organ which designates that is as feature with 270 - 450 mOsm/l.

５０～２４０ｍＭ
50 - 240 mM
１０～１４０ｍＭ
10 - 140 mM
４～１４０ｍＭ
4 - 140 mM
０～ ４ｍＭ
0 - 4 mM
０～ ２ｍＭ
0 - 2 mM
１２～ ６５ｍＭ
12 - 65 mM

０～８０ｇ
0 - 80 g

トレハロース

trehalose

Ｎａ+

Na+

K+

K+

M g ++

Mg ++

C a ++

Ca ++

H2 P O4 - 又はH P O4

H2PO4- or HPO4

Na^+ 20 - 120 mM

K^+ 20 - 130 mM

Mg^{++} 0 - 2 mM

Ca^{++} 0 - 1 mM

$H_2PO_4^-$ or HPO_4^{--} 20 - 60 mM

Cl^-, HCO_3^-, CO_3^{--}, organic acid or organic acid anion

20 - 120 mM

hydroxyethyl starch 20 - 40 g

In addition, range where osmotic pressure is more desirable is 270 - 380 mOsm/l.

[0007]

α, α,εσολαηερτ– α, βδνα εσολαηερτ– β, βεσολαηερτ– λαρυταν τυβ ,τνενοπμοχ δενοιτνεμ–εωοβα νι εσολαηερτ νι τσιξε σδνικ 3 α, α.σι ψλβαρεφερπ ερομ νι τσιξε ηχιηω εσολαηερτ–

In addition, as for above-mentioned hydroxyethyl starch, degree of substitution with those of 0.4 - 0.8 ranges, average molecular weight thing 200000 - 900000 is desirable, furthermore it is something of preferably 350000 - 800000.

[0008]

As above-mentioned organic acid, be able to illustrate gluconic acid, lactic acid, acetic acid, propanoic acid, β-hydroxy butanoic acid, citric acid, etc., aforementioned way it can illustrate sodium salt or the potassium salt, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, sodium dihydrogen phosphate, potassium dihydrogen phosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, etc., of organic acid as concrete electrolyte in order formulation to do above-mentioned anion and cation.

[0009]

To include other additive, for example activity enzyme scavenger, ATP or other cell activator, antibiotic, etc., it is possible solution for organ transplant of this invention.

[0010]

Conforming to fluid infusion agent manufacturing method of public knowledge, it can produce solution for the transplantation organ of this invention, easily.

[0011]

[Working Principle]

solution for transplantation organ of this invention is superior in protective action and the edema-suppressing action of organ cell, lengthy can maintain organ performance.

In addition, solution for transplantation organ of this invention has not used the unstable compound like insulin of UW solution component, it is a stability in pharmaceutical.

[0012]

[Working Example (s)]

Working Example 1

Approximately total amount was designated as 1000 ml and melting after α, α-trehalose 35 g, potassium chloride 1.12 g, potassium dihydrogen phosphate 2.05 g and dipotassium hydrogen phosphate 7.4 g, including sodium hydrogen carbonate 0.84 g and the distilled water in distilled water 800ml of 50 deg C.

It filtered this at once, after being filled and plugging, steam sterilization did in glass bottle and acquired solution for transplantation organ of osmotic pressure 271 mOsm/l, pH 7.46.

[0013]

Working Example 2

Approximately total amount was designated as 1000 ml and melting after α, α-trehalose 70 g, potassium chloride 1.12 g, potassium dihydrogen phosphate 2.05 g and dipotassium hydrogen phosphate 7.4 g, including sodium hydrogen carbonate 0.84 g and the distilled water in distilled water 800ml of 50 deg C.

It filtered this at once, after being filled and plugging, steam sterilization did in glass bottle and acquired solution for transplantation organ of osmotic pressure 373 mOsm/l, pH 7.42.

[0014]

Working Example 3

Approximately total amount was designated as 1000 ml α, α-trehalose 41 g, hydroxyethyl starch (average molecular weight 429000, degree of substitution 0.55) 30 g, sodium gluconate 21.81 g, potassium dihydrogen phosphate 0.885 g, and after melting dipotassium hydrogen phosphate 3.222 g, including distilled water in distilled water 800ml of 50 deg C.

It filtered this at once, after being filled and plugging, steam sterilization did in glass bottle and acquired solution for transplantation organ of osmotic pressure 366 mOsm/l, pH 7.35.

[0015]

Working Example 4

Approximately total amount was designated as 1000 ml α, α-trehalose 41 g, hydroxyethyl starch (average molecular weight 429000, degree of substitution 0.55), after melting sodium gluconate 4.362 g, potassium gluconate 20.263 g, potassium dihydrogen phosphate 0.885 g, and dipotassium hydrogen phosphate 3.222 g, including distilled water in distilled water 800ml of 50 deg C.

It filtered this at once, after being filled and plugging, steam sterilization did in glass bottle and acquired solution for transplantation organ of osmotic pressure 370 mOsm/l, pH 7.37.

[0016]

Left lung same place transplant technique was administered making use of mixed-breed adult dog, perfusion of organ and effect of preservation were inspected with solution for this invention transplantation organ.

[0017]

Test Example 1

method

Mixed-breed dog 34animals of body weight 7.6 - 13.2 kg, it made 17 groups from body height, body weight with 2 animals (Same reception dog as organ supply dog) which coincide as 1 -set, divided into 3 group (Class 1 5 sets, Class II 6 group and Class III 6 group) in random, offered to experiment below.

[0018]

First, narcotic after doing, following organ supply dog to drip method with Halothane, from left pulmonary artery, under condition of50 ml/ kg, 50cmH_2O, perfusion it did sample solution (In Class 1 you use aforementioned Euro-Collins solution for Working Example 2 solution, Class III in Working Example 1solution, Class II) of 8 - 10 deg C.

avulsion it did after perfusion, without separating heart and the left lung, in same sample solution 500ml of 8 - 10 deg C it soaked retained.

12 hours later, it excised left lung of organ reception dog under narcotic, followed to vise method and transplant did only the left lung of preservation.

reperfusion doing blood, 40 minutes, 70 minutes, clamp doing to stop right pulmonary artery in every 130 minute passage every time, to the conventional method following it measured arterial blood oxygen partial pressure and left pulmonary artery pressure.

[0019]

Next, death doing organ reception dog, it took preparation respectively from upper part lung leaf and bottom lung leaf of transplant lung, HE stain did in one for pathology finding.

Remaining upper part lung leaf and bottom lung leaf concerning respectively, weight before drying (wet weight) with weight (dried weight) after oven drying was measured, (wet weight)/ (dried weight) was sought.

[0020]

Result

measurement result of arterial blood oxygen partial pressure was shown in Table 1.

transplant lung ventilation talent of solution use group (Class 1, Class II) for this invention transplantation organ was maintained as many as130 minutes later well, it understood that it is superior more significantly than that of comparative group, namely Euro-Collins solution administration group (Class III).

[0021]

[Table 1]

1. Arterial blood oxygen partial pressure (mmHg)
2. Organ donor dog
3. Organ recipient dog (following left lung transplant and hemo-reperfusion)
4. Before extirpating left lung
5. After 40 minutes
6. After 70 minutes
7. After 130 minutes
8. Group I
9. Group II
10. Group III

動 脈 血 酸 素 分 圧（mmHg）

	臓器供給犬	臓器受容犬（左肺移植、血液再灌流後）		
	左肺摘出前	40分後	70分後	130分後
I 群	281.8 ±10.6	283.4 ±14.0	277.5 ±19.9	264.9 ±26.2
II 群	287.6 ± 6.7	302.2 ±14.7	287.9 ±18.8	257.5 ±33.0
III 群	283.9 ± 3.4	162.9 ±44.5	135.1 ±40.8	114.8 ±49.2

[0022]

artery pressure measurement result of transplant lung was shown in Table 2, but the significant difference is recognized between 3 groups and in is.

But, it could recognize low tendency in order of Class II, Class 1, Class III.

[0023]

[Table 2]

1. Arterial pressure in transplanted lung (mmHg)
2. Organ recipient dog (following left lung transplant and hemo-reperfusion)
3. After 40 minutes
5. After 70 minutes
6. After 130 minutes
7. Group I
8. Group II
9. Group III

移植肺の動脈圧（mmHg）

	臓器受容犬（左肺移植、血液再灌流後）		
	40分後	70分後	130分後
I 群	36.4 ± 2.2	35.0 ± 1.4	31.2 ± 2.0
II 群	34.2 ± 4.7	30.3 ± 4.6	30.3 ± 2.5
III 群	41.6 ± 7.0	39.4 ± 6.7	40.8 ± 6.8
I 群	36.4 ± 2.2	35.0 ± 1.4	31.2 ± 2.0
II 群	34.2 ± 4.7	30.3 ± 4.6	30.3 ± 2.5
III 群	41.6 ± 7.0	39.4 ± 6.7	40.8 ± 6.8

[0024]

In Table 3, (wet weight) / (dried weight) was calculated as one of indicator which reflects extent of edema of transplant lung, result was shown.

Similarity to description above, significant difference was not recognized between3 groups, but it could recognize tendency whose extent of edema is low in order of Class 1, Class II, Class III.

[0025]

[Table 3]
1. Transplanted lung (wet weight) / (dry weight)
2. Group I
3. Group II
4. Group III

移植肺の（湿重量）／（乾燥重量）

I 群	6．21±0．64
II 群	6．50±0．20
III 群	8．43±1．14

[0026]

Result of preparation observation of HE stain, concerning Class 1 and the Class II, all example was normal lung structure almost.

But, as 6 example medium 5 examples it could recognize partial edema characteristic change as severe, remaining 1 example concerning the Class III.

[0027]

Test Example 2

method

Mixed-breed dog 22 animals of body weight 7.7 - 12.9 kg, it made 11 groups from body height, body weight with 2 animals (Same reception dog as organ supply dog) which coincide as 1 -set, divided into 2 sets (Class IV 5 sets, V group 6 set) in random, to similar to Test Example 1 (You use Euro-Collins solution for Working Example 3 solution, V group in Class IV), it soaked it retained heart and left lung.

20 hours later, transplant doing left lung, reperfusion it did the blood, 40 minutes, 70 minutes, measured arterial blood oxygen partial pressure and pulmonary artery pressure in every 130 minute passage.

Furthermore, after 130 minutes passage concerning blood vessel resistance of the left lung it measured.

Furthermore, left lung preparation HE stain was done in same way as the Test Example 1, remaining (wet weight) / (dried weight) was sought.

[0028]

measurement result of arterial blood oxygen partial pressure was shown in Table 4.

transplant lung ventilation talent of solution use group (Class IV) for this invention transplantation organ was maintained as many as130 minutes later well, from that of comparative group, namely Jo row Collins fluid administration group (V group), it understood that it is superior significantly.

[0029]

[Table 4]

1. Arterial blood oxygen partial pressure (mmHg)
2. Organ donor dog
3. Organ recipient dog (following left lung transplant and hemo-reperfusion)
4. Before extirpating left lung
5. After 40 minutes
6. After 70 minutes
7. After 130 minutes
8. Group IV
9. Group V

動 脈 血 酸 素 分 圧（mmHg）

	臓器供給犬	臓器受容犬（左肺移植、血液再灌流後）		
	左肺摘出前	４０分後	７０分後	１３０分後
IV 群	316.9 ±26.0	291.5 ± 6.5	299.8 ± 7.5	292.3 ±20.1
V 群	294.9 ± 9.0	92.1 ±23.7	96.5 ±29.6	80.5 ±20.8

[0030]

artery pressure measurement result of transplant lung was shown in Table 5.

significant difference was not recognized between 2 sets, but as for artery pressure of Class IV it could recognize tendency which is lower than that of V group.

[0031]

[Table 5]
1. Arterial pressure in transplanted lung (mmHg)
2. Organ recipient dog (following left lung transplant and hemo-reperfusion)
3. After 40 minutes
5. After 70 minutes
6. After 130 minutes
7. Group IV
8. Group V

移植肺の動脈圧（mmHg）

	臓器受容犬（左肺移植、血液再灌流後）		
	４０分後	７０分後	１３０分後
IV 群	26.0 ± 4.3	23.4 ± 4.4	26.8 ± 6.4
V 群	35.4 ± 3.0	29.8 ± 2.3	34.0 ± 3.8

[0032]

blood vessel resistance measurement result of transplant left lung was shown in Table 6.

As for blood vessel hardening modified extent of Class IV it understood that it is lower than that of V group significantly.

[0033]

[Table 6]

移植肺の血管抵抗 (dynes・sec ・cm^{-5})

	臓器供給犬 (左肺摘出前)	臓器受容犬(左肺移植、 血液再灌流、１３０分後)
IV 群	４４７．６±１２５．８	６８２．２±２８７．６
V 群	４９５．３±１０７．２	２２３５．７±２９７．６

1. Arterial resistance in transplanted lung (dynes•sec•cm^{-5})
2. Organ donor dog (efore extirpating left lung)
3. Organ recipient dog (130 minutes following left lung transplant and hemo-reperfusion)
4. Group IV
5. Group V

[0034]

(wet weight) / (dried weight) was calculated in Table 7, result was shown.

As for extent of edema of Class IV it understood that it is lower than that of V group significantly.

[0035]

[Table 7]
1. Transplanted lung (wet weight) / (dry weight)
2. Group IV
3. Group V

移植肺の（湿重量）／（乾燥重量）

IV 群	5．7±0．3
V 群	8．1±0．5

[0036]

Result of preparation observation of HE stain, concerning Class IV, all example was normal lung structure almost.

But, it could recognize severe edema characteristic change as all example concerning V group.

[0037]

From test result above, as for solution for this invention transplantation organ, showing the effect which is superior in organ function maintenance was ascertained.

Furthermore even among them, K^+ concentration with approximately half or below of the Na^+concentration, as for solution (Working Example 3 solution) which adds hydroxyethyl starch, with 20 hour preservation it understood that marked effect is shown.

[0038]

[Effects of the Invention]

According to this invention, without impairing cord function of the organ for transplant, perfusion and lengthy preservation to be possible, furthermore solution for stable transplantation organ can be offered to pharmaceutical.

PATENT ABSTRACTS OF JAPAN

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(22)Date of filing : **24.07.1992**

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(54) SOLUTION FOR INTERNAL ORGANS TO BE TRANSPLANTED

(57)Abstract:
PURPOSE: To provide a solution for the internal organs to be transplanted which enables perfusion and storage for a long period of time without any damage in the functions of the organs.
CONSTITUTION: The solution for internal organs to be transplanted contains, in 1,000ml aqueous solution, 50 to 240mM of trehalose, 10 to 40mM of Na+, 4 to 140mM of K+, 0 to 4mM of Mg++, 0 to 2mM of Ca++, 12 to 65mM of H2PO4- or HPO4--, 15-150mM of Cl-, HCO-, CO3--, organic acid or organic acid anion, and 0 to 80g of hydroxyethylstarch, and has 270 to 450mOsm/l osmotic pressure and pH 7 to 8.

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CLAIMS

[Claim(s)]
[Claim 1] The solution for transplants with which the following component is contained within the limits of the following at least among 1000ml water solution, and osmotic pressure is characterized by pH being 7-8 by 270 - 450 mOsm/l.
Trehalose 50-240mM Na+ 10-140mM K+ 4-140mM Mg++ 0- 4mM calcium++ 0- 2mM H2 PO4 - Or HPO4-- 12-65mM Cl-, HCO3-, CO3--, an organic acid, or organic-acid anion 15 - 150mM hydroxyethyl starch 0-80g

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the solution which uses the organ for transplantation perfusion or since it saves in more detail about the solution for transplants.
[0002]
[Description of the Prior Art] Euro which contains potassium chloride, a potassium dihydrogenphosphate, the potassium phosphate, a sodium hydrogencarbonate, and grape sugar in one of the solutions for transplants most often conventionally used in the West - Collins (Euro-Collins) There is liquid. However, although this solution can be used for the high kidney of the functional maintenance force, about other organs, it cannot be said to be enough [the protective action to the denaturation of a cell], but has the problem that the maintenance time amount of an organ function is short. Hydroxyethyl starch was contained as sodium lactobionate, a raffinose, and a colloid osmotic agent as a non-penetrating agent, and the electrolytic solution and UW liquid (JP,1-246201,A) with which the adenosine, the insulin, etc. were further added in consideration of the energy metabolism of a cell were recently developed. However, this solution has a difficulty in galenical pharmacy-stability and has problems, such as needing cold storage.
[0003]
[Problem(s) to be Solved by the Invention] Therefore, in the organ for transplantation, the technical problem of this invention is perfusion or a solution for saving, is excellent in a maintenance operation of an organ function, and is to offer a solution stable in galenical pharmacy moreover.
[0004]
[Means for Solving the Problem] this invention persons were able to complete this invention which solves the above-mentioned technical problem, as a result of taking lessons from those combination and blending ratio of coal and inquiring wholeheartedly using various electrolytes, osmoregulating chemicals, colloid osmotic agents, and cell membrane stabilizers.
[0005] That is, this invention contains the following component within the limits of the following at least among 1000ml water solution, and osmotic pressure offers the solution for transplants characterized by pH being 7-8 by 270 - 450 mOsm/l.

Trehalose 50-240mM Na+ 10-140mM K+ 4-140mM Mg++ 0- 4mM calcium++ 0- mM H2 PO4 - Or HPO4-- 12-65mM Cl-, HCO3-, CO3--, an organic acid, or organic-acid anion 15 - 150mM hydroxyethyl starch 0-80g [0006] It will be as follows if the presentation range of the more desirable embodiment of this invention (inside of 1000ml water solution) is shown. Trehalose 100-210mM Na+ 20-120mM K+ 20-130mM Mg++ 0- 2mM calcium++ 0- mM H2 PO4 - Or HPO4-- 20- 60mM Cl-, HCO3-, CO3--, an organic acid, or organic-acid anion 20 - 120mM hydroxyethyl starch 20- The more desirable range of osmotic pressure of 40g is 270 - 380 mOsm/l again.

[0007] Although three sorts of alpha and alpha-trehalose, alpha, and beta-trehalose and beta, and beta-trehalose exist in the trehalose in the above-mentioned component, it is alpha and alpha-trehalose which exists naturally more preferably. Moreover, the above-mentioned hydroxyethyl starch is the thing of the range of 0.4-0.8, the thing of 200000-900000 is [average molecular weight] desirable still more desirable, and, as for it, whenever [permutation] is the thing of 350000-800000.

[0008] As the above-mentioned organic acid, a gluconic acid, a lactic acid, an acetic acid, a propionic acid, beta-hydroxybutyric acid, a citric acid, etc. can be illustrated, and the above sodium salt of an organic acid or potassium salt, a sodium chloride, potassium chloride, a magnesium chloride, a calcium chloride, a sodium dihydrogenphosphate, a potassium dihydrogenphosphate, disodium hydrogenphosphate, the potassium phosphate, a sodium hydrogencarbonate, a potassium hydrogencarbonate, a sodium carbonate, potassium carbonate, etc. can be illustrated as a concrete electrolyte for prescribing the above-mentioned anion and a cation.

[0009] The solution for organ transplantations of this invention can contain cell activators, such as other additives, for example, an active oxygen elimination agent, and ATP, an antibiotic, etc.

[0010] The solution for transplants of this invention can be easily manufactured based on the well-known transfusions manufacture approach.

[0011]

[Function] The solution for transplants of this invention is excellent in the protective action and edema depressant action of an organ cell, and can maintain the organ function for a long time. Moreover, an unstable compound like the insulin of UW liquid component is not used for the solution for transplants of this invention, but it is stable in galenical pharmacy.

[0012]

[Example]

After dissolving alpha and alpha-trehalose 35g, 1.12g of potassium chloride, 2.05g of potassium dihydrogenphosphates, and 7.4g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 1 abbreviation, 0.84g of sodium hydrogencarbonates and distilled water were added, and the whole quantity was set to 1000ml. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 271 mOsm/l and pH7.46 was obtained.

[0013] After dissolving alpha and alpha-trehalose 70g, 1.12g of potassium chloride, 2.05g of potassium dihydrogenphosphates, and 7.4g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 2 abbreviation, 0.84g of sodium hydrogencarbonates and distilled water were added, and the whole quantity was set to 1000ml. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 373 mOsm/l and pH7.42 was obtained.

[0014] Distilled water was added and the whole quantity was set to 1000ml, after dissolving alpha and alpha-trehalose 41g, 30g (whenever [average-molecular-weight 429000 and permutation] 0.55) of hydroxyethyl starch, 21.81g of sodium gluconate, 0.885g of potassium dihydrogenphosphates, and

3.222g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 3 abbreviation. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 366 mOsm/l and pH7.35 was obtained.
[0015] Distilled water was added and the whole quantity was set to 1000ml, after dissolving alpha and alpha-trehalose 41g, hydroxyethyl starch (whenever [average-molecular-weight 429000 and permutation] 0.55), 4.362g of sodium gluconate, 20.263g of potassium gluconate, 0.885g of potassium dihydrogenphosphates, and 3.222g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 4 abbreviation. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 370 mOsm/l and pH7.37 was obtained.
[0016] The pulmo-sinister orthotopic-graft way was given using the crossbred adult dog, and the effectiveness of preservation in the perfusion list of the organ by the solution for this invention transplants was investigated.
[0017] 2 with which height and weight agree more 34 mongrels with an example of trial 1 approach weight of 7.6-13.2kg ** (an organ supply dog and this acceptance dog) It was made 1 set, considered as 17 sets, and divided into three groups (5 sets of I groups, 6 sets of II groups, and III group 6 group) at random, and the following experiments were presented.
[0018] First, after anesthetizing an organ supply dog by halothane, according to the drip method, perfusion of the 8-10-degree C test solution (it is [group / I] said Euro to example 2 liquid and an III group in example 1 liquid and II group - Collins liquid is used) was carried out under [left pulmonaly artery] the condition of 50 ml/kg and 50cmH2 O. It extracted after perfusion, without separating the pulmo sinister from the heart, and immersion preservation was carried out at 500ml of these 8-10-degree C test solution. It excised under anesthesia of the pulmo sinister of an organ acceptance dog 12 hours after, and only the pulmo sinister of preservation was transplanted according to the vice method. Reperfusion of the blood was carried out, the clamp stop of the right pulmonary artery was carried out for every progress for 40 minutes, 70 minutes, and 130 minutes, and arterial oxygen tension and a pulmo-sinister arterial blood pressure were measured each time according to the conventional method.
[0019] Next, beneficial death of the organ acceptance dog was carried out, the sample was taken, respectively from the up lobe of the lung and lower lobe of the lung of transplantation lungs, and hematoxylin eosin staining was carried out to pathological findings. About the remaining up lobe of the lung and each lower lobe of the lung, the weight before desiccation (wet weight) and the weight after an oven drying (dry weight) were measured, and it asked for (wet weight)/(dry weight).
[0020] The measurement result of arterial oxygen tension was shown in the result table 1. After 130 minutes is often maintained and the transplantation pulmonary ventilatory capacity of the solution use group for this invention transplants (I group, II group) is a comparison group, i.e., Euro. - It turned out that that of a Collins liquid administration group (III group) is excelled intentionally.
[0021]
[Table 1]

[0022] Although the arterial-pressure-determination result of transplantation lungs was shown in Table 2, a significant difference is accepted in 3 between groups, and it is inside **. However, II group, I group, and III The low inclination was accepted in order of the group.
[0023]
[Table 2]

[0024] (Wet weight)/(dry weight) was computed to Table 3 as one of the indexes reflecting extent of the edema of transplantation lungs, and the result was shown in it. Like the above, although the significant difference was not accepted in 3 between groups, they are I group, II group, and III. The inclination for extent of an edema to be low was accepted in order of the group.
[0025]
[Table 3]

[0026] It was lung structure with all examples almost normal about I group and II group as a result of sample observation of hematoxylin eosin staining. However, III About the group, the critical remaining edema nature change partial to one example was accepted in five examples among six examples.
[0027] 2 with which height and weight agree more 22 mongrels with an example of trial 2 approach weight of 7.7-12.9kg ** (an organ supply dog and this acceptance dog) Make it 1 set and it considers as 11 sets. It divided into two groups (5 sets of IV groups, 6 sets of V groups) at random, and immersion preservation of the heart and the pulmo sinister was carried out like the example 1 of a trial (it is Euro to example 3 liquid and V group in IV group - Collins liquid is used). 20 hours after, the pulmo sinister was transplanted, reperfusion of the blood was carried out, and arterial oxygen tension and a pulmonary artery pressure were measured for every progress for 40 minutes, 70 minutes, and 130 minutes. In addition, after 130-minute progress, it measured also about the vascular resistance of the pulmo sinister. Furthermore, hematoxylin eosin staining of the pulmo-sinister sample was carried out like the example 1 of a trial, and it asked for remaining (wet weight)/(dry weight).
[0028] The measurement result of arterial oxygen tension was shown in Table 4. After 130 minutes is often maintained and the transplantation pulmonary ventilatory capacity of the solution use group for this invention transplants (IV group) is a comparison group, i.e., Euro. - It turned out that that of a Collins liquid administration group (V group) is excelled intentionally.
[0029]
[Table 4]

[0030] The arterial-pressure-determination result of transplantation lungs was shown in Table 5. Although the significant difference was not accepted in 2 between groups, the inclination for the arterial blood pressure of IV group to be lower than that of V group was accepted.
[0031]
[Table 5]

[0032] The vascular resistance measurement result of the transplantation pulmo sinister was shown in Table 6. It turned out that extent of the angiosclerosis denaturation of IV group is more nearly intentionally [than that of V group] low.
[0033]
[Table 6]

[0034] (Wet weight)/(dry weight) was computed to Table 7, and the result was shown in it. It turned out that extent of the edema of IV group is more nearly intentionally [than that of V group] low.
[0035]
[Table 7]

[0036] It was lung structure with all examples almost normal about IV group as a result of sample observation of hematoxylin eosin staining. However, about V group, a critical edema nature change

was accepted in all examples.
[0037] From the above test result, it became clear that the solution for this invention transplants showed the effectiveness excellent in organ functional maintenance. Especially, it is K+. Concentration is Na+. It turned out that the solution (example 3 liquid) which added hydroxyethyl starch below in abbreviation one half of concentration shows still more remarkable effectiveness by preservation for 20 hours.
[0038]
[Effect of the Invention] According to this invention, perfusion and prolonged preservation can be performed without spoiling the clue function of the organ for transplantation, and, moreover, the solution for transplants stable in galenical pharmacy can be offered.

TECHNICAL FIELD

[Industrial Application] This invention relates to the solution which uses the organ for transplantation perfusion or since it saves in more detail about the solution for transplants.

PRIOR ART

[Description of the Prior Art] Euro which contains potassium chloride, a potassium dihydrogenphosphate, the potassium phosphate, a sodium hydrogencarbonate, and grape sugar in one of the solutions for transplants most often conventionally used in the West - Collins (Euro-Collins) There is liquid. However, although this solution can be used for the high kidney of the functional maintenance force, about other organs, it cannot be said to be enough [the protective action to the denaturation of a cell], but has the problem that the maintenance time amount of an organ function is short. Hydroxyethyl starch was contained as sodium lactobionate, a raffinose, and a colloid osmotic agent as a non-penetrating agent, and the electrolytic solution and UW liquid (JP,1-246201,A) with which the adenosine, the insulin, etc. were further added in consideration of the energy metabolism of a cell were recently developed. However, this solution has a difficulty in galenical pharmacy-stability and has problems, such as needing cold storage.

EFFECT OF THE INVENTION

[Effect of the Invention] According to this invention, perfusion and prolonged preservation can be performed without spoiling the clue function of the organ for transplantation, and, moreover, the solution for transplants stable in galenical pharmacy can be offered.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] Therefore, in the organ for transplantation, the technical problem of this invention is perfusion or a solution for saving, is excellent in a maintenance operation of an organ function, and is to offer a solution stable in galenical pharmacy moreover.

MEANS

[Means for Solving the Problem] this invention persons were able to complete this invention which solves the above-mentioned technical problem, as a result of taking lessons from those combination and blending ratio of coal and inquiring wholeheartedly using various electrolytes, osmoregulating chemicals, colloid osmotic agents, and cell membrane stabilizers.
[0005] That is, this invention contains the following component within the limits of the following at least among 1000ml water solution, and osmotic pressure offers the solution for transplants characterized by pH being 7-8 by 270 - 450 mOsm/l.
Trehalose 50-240mM Na+ 10-140mM K+ 4-140mM Mg++ 0- 4mM calcium++ 0- mM H2 PO4 - Or HPO4-- 12-65mM Cl-, HCO3-, CO3--, an organic acid, or organic-acid anion 15 - 150mM hydroxyethyl starch 0-80g [0006] It will be as follows if the presentation range of the more desirable embodiment of this invention (inside of 1000ml water solution) is shown.
Trehalose 100-210mM Na+ 20-120mM K+ 20-130mM Mg++ 0- 2mM calcium++ 0- mM H2 PO4 - Or HPO4-- 20- 60mM Cl-, HCO3-, CO3--, an organic acid, or organic-acid anion 20 - 120mM hydroxyethyl starch 20- The more desirable range of osmotic pressure of 40g is 270 - 380 mOsm/l again.
[0007] Although three sorts of alpha and alpha-trehalose, alpha, and beta-trehalose and beta, and beta-trehalose exist in the trehalose in the above-mentioned component, it is alpha and alpha-trehalose which exists naturally more preferably. Moreover, the above-mentioned hydroxyethyl starch is the thing of the range of 0.4-0.8, the thing of 200000-900000 is [average molecular weight] desirable still more desirable, and, as for it, whenever [permutation] is the thing of 350000-800000.
[0008] As the above-mentioned organic acid, a gluconic acid, a lactic acid, an acetic acid, a propionic acid, beta-hydroxybutyric acid, a citric acid, etc. can be illustrated, and the above sodium salt of an organic acid or potassium salt, a sodium chloride, potassium chloride, a magnesium chloride, a calcium chloride, a sodium dihydrogenphosphate, a potassium dihydrogenphosphate, disodium hydrogenphosphate, the potassium phosphate, a sodium hydrogencarbonate, a potassium hydrogencarbonate, a sodium carbonate, potassium carbonate, etc. can be illustrated as a concrete electrolyte for prescribing the above-mentioned anion and a cation.
[0009] The solution for organ transplantations of this invention can contain cell activators, such as other additives, for example, an active oxygen elimination agent, and ATP, an antibiotic, etc.
[0010] The solution for transplants of this invention can be easily manufactured based on the well-known transfusions manufacture approach.

OPERATION

[Function] The solution for transplants of this invention is excellent in the protective action and edema depressant action of an organ cell, and can maintain the organ function for a long time. Moreover, an

unstable compound like the insulin of UW liquid component is not used for the solution for transplants of this invention, but it is stable in galenical pharmacy.

EXAMPLE

[Example]
After dissolving alpha and alpha-trehalose 35g, 1.12g of potassium chloride, 2.05g of potassium dihydrogenphosphates, and 7.4g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 1 abbreviation, 0.84g of sodium hydrogencarbonates and distilled water were added, and the whole quantity was set to 1000ml. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 271 mOsm/l and pH7.46 was obtained.
[0013] After dissolving alpha and alpha-trehalose 70g, 1.12g of potassium chloride, 2.05g of potassium dihydrogenphosphates, and 7.4g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 2 abbreviation, 0.84g of sodium hydrogencarbonates and distilled water were added, and the whole quantity was set to 1000ml. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 373 mOsm/l and pH7.42 was obtained.
[0014] Distilled water was added and the whole quantity was set to 1000ml, after dissolving alpha and alpha-trehalose 41g, 30g (whenever [average-molecular-weight 429000 and permutation] 0.55) of hydroxyethyl starch, 21.81g of sodium gluconate, 0.885g of potassium dihydrogenphosphates, and 3.222g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 3 abbreviation. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 366 mOsm/l and pH7.35 was obtained.
[0015] Distilled water was added and the whole quantity was set to 1000ml, after dissolving alpha and alpha-trehalose 41g, hydroxyethyl starch (whenever [average-molecular-weight 429000 and permutation] 0.55), 4.362g of sodium gluconate, 20.263g of potassium gluconate, 0.885g of potassium dihydrogenphosphates, and 3.222g of potassium phosphate in 800ml of distilled water of 50 degrees C of example 4 abbreviation. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 370 mOsm/l and pH7.37 was obtained.
[0016] The pulmo-sinister orthotopic-graft way was given using the crossbred adult dog, and the effectiveness of preservation in the perfusion list of the organ by the solution for this invention transplants was investigated.
[0017] 2 with which height and weight agree more 34 mongrels with an example of trial 1 approach weight of 7.6-13.2kg ** (an organ supply dog and this acceptance dog) It was made 1 set, considered as 17 sets, and divided into three groups (5 sets of I groups, 6 sets of II groups, and III group 6 group) at random, and the following experiments were presented.
[0018] First, after anesthetizing an organ supply dog by halothane, according to the drip method, perfusion of the 8-10-degree C test solution (it is [group / I] said Euro to example 2 liquid and an III group in example 1 liquid and II group - Collins liquid is used) was carried out under [left pulmonaly artery] the condition of 50 ml/kg and 50cmH2 O. It extracted after perfusion, without separating the pulmo sinister from the heart, and immersion preservation was carried out at 500ml of these 8-10-degree C test solution. It excised under anesthesia of the pulmo sinister of an organ acceptance dog 12

hours after, and only the pulmo sinister of preservation was transplanted according to the vice method. Reperfusion of the blood was carried out, the clamp stop of the right pulmonary artery was carried out for every progress for 40 minutes, 70 minutes, and 130 minutes, and arterial oxygen tension and a pulmo-sinister arterial blood pressure were measured each time according to the conventional method. [0019] Next, beneficial death of the organ acceptance dog was carried out, the sample was taken, respectively from the up lobe of the lung and lower lobe of the lung of transplantation lungs, and hematoxylin eosin staining was carried out to pathological findings. About the remaining up lobe of the lung and each lower lobe of the lung, the weight before desiccation (wet weight) and the weight after an oven drying (dry weight) were measured, and it asked for (wet weight)/(dry weight). [0020] The measurement result of arterial oxygen tension was shown in the result table 1. After 130 minutes is often maintained and the transplantation pulmonary ventilatory capacity of the solution use group for this invention transplants (I group, II group) is a comparison group, i.e., Euro. - It turned out that that of a Collins liquid administration group (III group) is excelled intentionally. [0021]
[Table 1]

[0022] Although the arterial-pressure-determination result of transplantation lungs was shown in Table 2, a significant difference is accepted in 3 between groups, and it is inside **. However, II group, I group, and III The low inclination was accepted in order of the group. [0023]
[Table 2]

[0024] (Wet weight)/(dry weight) was computed to Table 3 as one of the indexes reflecting extent of the edema of transplantation lungs, and the result was shown in it. Like the above, although the significant difference was not accepted in 3 between groups, they are I group, II group, and III. The inclination for extent of an edema to be low was accepted in order of the group. [0025]
[Table 3]

[0026] It was lung structure with all examples almost normal about I group and II group as a result of sample observation of hematoxylin eosin staining. However, III About the group, the critical remaining edema nature change partial to one example was accepted in five examples among six examples. [0027] 2 with which height and weight agree more 22 mongrels with an example of trial 2 approach weight of 7.7-12.9kg ** (an organ supply dog and this acceptance dog) Make it 1 set and it considers as 11 sets. It divided into two groups (5 sets of IV groups, 6 sets of V groups) at random, and immersion preservation of the heart and the pulmo sinister was carried out like the example 1 of a trial (it is Euro to example 3 liquid and V group in IV group - Collins liquid is used). 20 hours after, the pulmo sinister was transplanted, reperfusion of the blood was carried out, and arterial oxygen tension and a pulmonary artery pressure were measured for every progress for 40 minutes, 70 minutes, and 130 minutes. In addition, after 130-minute progress, it measured also about the vascular resistance of the pulmo sinister. Furthermore, hematoxylin eosin staining of the pulmo-sinister sample was carried out like the example 1 of a trial, and it asked for remaining (wet weight)/(dry weight). [0028] The measurement result of arterial oxygen tension was shown in Table 4. After 130 minutes is often maintained and the transplantation pulmonary ventilatory capacity of the solution use group for this invention transplants (IV group) is a comparison group, i.e., Euro. - It turned out that that of a Collins liquid administration group (V group) is excelled intentionally.

[0029]
[Table 4]

[0030] The arterial-pressure-determination result of transplantation lungs was shown in Table 5. Although the significant difference was not accepted in 2 between groups, the inclination for the arterial blood pressure of IV group to be lower than that of V group was accepted.
[0031]
[Table 5]

[0032] The vascular resistance measurement result of the transplantation pulmo sinister was shown in Table 6. It turned out that extent of the angiosclerosis denaturation of IV group is more nearly intentionally [than that of V group] low.
[0033]
[Table 6]

[0034] (Wet weight)/(dry weight) was computed to Table 7, and the result was shown in it. It turned out that extent of the edema of IV group is more nearly intentionally [than that of V group] low.
[0035]
[Table 7]

[0036] It was lung structure with all examples almost normal about IV group as a result of sample observation of hematoxylin eosin staining. However, about V group, a critical edema nature change was accepted in all examples.
[0037] From the above test result, it became clear that the solution for this invention transplants showed the effectiveness excellent in organ functional maintenance. Especially, it is K+. Concentration is Na+. It turned out that the solution (example 3 liquid) which added hydroxyethyl starch below in abbreviation one half of concentration shows still more remarkable effectiveness by preservation for 20 hours.

CORRECTION OR AMENDMENT

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[Procedure amendment 1]
[Document to be Amended] Specification
[Item(s) to be Amended] Claim
[Method of Amendment] Modification
[Proposed Amendment]
[Claim(s)]
[Claim 1] The solution for transplants with which the following component is contained within the limits of the following at least among 1000ml water solution, and osmotic pressure is characterized by pH being 7-8 by 270 - 450 mOsm/l.
Trehalose 50-240mM
Na+ 10-140mM
K+ 4-140mM
H2PO4- or HPO4 -- 12-65mM
Cl-, and HCO3, -, CO3 --, an organic acid, or organic-acid anion 15-150mM
[Claim 2] Furthermore, the solution for transplants according to claim 1 which contains 80g or less of hydroxyethyl starch in said 1000ml water solution.
[Claim 3] The solution for transplants according to claim 2 whose content of said hydroxyethyl starch is 20g or more 40g or less.
[Claim 4] Furthermore, the solution for transplants according to claim 1 to 3 which contains respectively 4 or less mMs and/or 2 or less mMs calcium++ for Mg++ in said 1000ml water solution.
[Claim 5] The solution for transplants according to claim 1 to 4 which has osmotic pressure within the limits of 270 - 380 mOsm/l.
[Procedure amendment 2]
[Document to be Amended] Specification
[Item(s) to be Amended] 0002
[Method of Amendment] Modification
[Proposed Amendment]

[0002]
[Description of the Prior Art] An organ transplantation has another organization, the organization which does not require angiostomy for the purpose of removing an organ and aiming at functional recovery or transplantation (a cornea, the skin graft, a bone marrow transplantation, etc.) of a cell, and the transplantation which needs revascularization instead of a function being the organization and organ which were fallen and abolished (the Nanzando medicine great dictionary, 1990). The Euro-Collins (Euro-Collins) liquid containing potassium chloride, a potassium dihydrogenphosphate, the potassium phosphate, a sodium hydrogencarbonate, and grape sugar is in one of the solutions for transplants most often conventionally used in the West. However, although this solution can be used for the high kidney of the functional maintenance force, about other organs, it cannot be said to be enough [the protective action to the denaturation of a cell], but has the problem that the maintenance time amount of an organ function is short. Hydroxyethyl starch was contained as sodium lactobionate, a raffinose, and a colloid osmotic agent as a non-penetrating agent, and the electrolytic solution and UW liquid (JP,1-246201,A) with which the adenosine, the insulin, etc. were further added in consideration of the energy metabolism of a cell were recently developed. However, this solution has a difficulty in galenical pharmacy-stability and has problems, such as needing cold storage.
[Procedure amendment 3]
[Document to be Amended] Specification
[Item(s) to be Amended] 0005
[Method of Amendment] Modification
[Proposed Amendment]
[0005] That is, this invention contains the following component within the limits of the following at least among 1000ml water solution, and osmotic pressure offers the solution for transplants characterized by pH being 7-8 by 270 - 450 mOsm/l.
Trehalose 50-240mM
Na+ 10-140mM
K+ 4-140mM
H2PO4- or HPO4 -- 12-65mM
Cl-, and HCO3, -, CO3 --, an organic acid, or organic-acid anion 15-150mM

However, it is desirable when 80g or less of hydroxyethyl starch (henceforth "HES") is made to contain in 1000ml water solution if needed. Moreover, less than [Mg++4mM] and/or less than [calcium++2mM] other than the above-mentioned sodium ion or calcium ion may be made to contain also as an electrolytic cation.
[Procedure amendment 4]
[Document to be Amended] Specification
[Item(s) to be Amended] 0006
[Method of Amendment] Modification
[Proposed Amendment]
[0006] It will be as follows if the presentation range of the more desirable embodiment of this invention (inside of 1000ml water solution) is shown.
Trehalose 100-210mM
Na+ 20-120mM
K+ 20-130mM
H2PO4- or HPO4 -- 20-60mM
Cl-, and HCO3, -, CO3 --, an organic acid, or organic-acid anion 20-120mM

Furthermore, when making the solution for transplants of this invention contain any one or more sorts in Mg++, calcium++, and hydroxyethyl starch, desirable contents (inside of 1000ml water solution) are less than [Mg++2mM], less than [calcium++1mM], and hydroxyethyl starch 20-40g, respectively. Moreover, the more desirable range of osmotic pressure is 270 - 380 mOsm/l.
[Procedure amendment 5]
[Document to be Amended] Specification
[Item(s) to be Amended] 0015
[Method of Amendment] Modification
[Proposed Amendment]
[0015] Example 4
Distilled water was added and the whole quantity was set to 1000ml, after dissolving alpha and alpha-trehalose 41g, 30g (whenever [average-molecular-weight 429000 and permutation] 0.55) of hydroxyethyl starch, 4.362g of sodium gluconate, 20.263g of potassium gluconate, 0.885g of potassium dihydrogenphosphates, and 3.222g of potassium phosphate in 800ml of about 50-degree C distilled water. This was filtered immediately, to the carboy, after restoration and sealing, wet sterilization was carried out and the solution for transplants of osmotic-pressure 370 mOsm/l and pH7.37 was obtained.
[Procedure amendment 6]
[Document to be Amended] Specification
[Item(s) to be Amended] 0016
[Method of Amendment] Modification
[Proposed Amendment]
[0016] The pulmo-sinister orthotopic-graft way was given using the crossbred adult dog, and the effectiveness of preservation in the perfusion list of the organ by the solution for this invention transplants was investigated. In addition, the constituent concentration of the solution for transplants of examples 1-4 is as having indicated to the below-mentioned table 8.
[Procedure amendment 7]
[Document to be Amended] Specification
[Item(s) to be Amended] 0036
[Method of Amendment] Modification
[Proposed Amendment]
[0036] It was lung structure with all examples almost normal about IV group as a result of sample observation of hematoxylin eosin staining. However, about V group, a critical edema nature change was accepted in all examples. The constituent concentration of the solution of the above example is as in Table 8.
[Table 8]